UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/803,223 | 03/09/2001 | Robert Korngold | KOR01-NP002 | 6791 |

24358 7590 08/20/2002

THOMAS JEFFERSON UNIVERSITY
INTELLECTUAL PROPERTY DIVISION
1020 WALNUT STREET
SUITE 620
PHILADELPHIA, PA 19107

| EXAMINER | |
|---|---|
| EWOLDT, GERALD R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 3 |

DATE MAILED: 08/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/803,223 | Korngold et al. |
| **Examiner** | **Art Unit** |
| G.R. Ewoldt | 1644 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Jan 29, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

**DETAILED ACTION**

1. Claims 1-5 are pending and being acted upon.

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because it does not include the mailing addresses nor residences of the Inventors.

A new declaration properly executed by all inventors is required. See MPEP §§ 608.04(b).

3. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

4. New corrected drawings must be filed with the changes incorporated therein. See the attached PTO Form-948. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections. Note that the filing of corrected drawings may no longer be held in abeyance until such time as claims are found allowable. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

5. Claims 1-5 are objected to because of the following informalities:

A) Claims 1 and 5 recite "T-cells" whereas Claim 2 recites "T cell". Applicant is advised that T cell is proper, however, Applicant is requested to pick either form for consistent recitation.

B) Claims 1 and 5 recite a list "comprising", absent any punctuation after "comprising". Applicant is advised that a colon (:) should properly follow the word.

C) Part c) in Claim 5 should properly end with a semi-colon (;).

Appropriate correction is required.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) the recitation of the phrase "eliminating selective cytotoxic T-cells," in Claims 1 and 5 is vague and indefinite as it is unclear just what a "selective cytotoxic T-cell" is, and what it is not, i.e, which cytotoxic T cells are encompassed by the claim and which are not. For prior art purposes however, the

phrase is considered to mean "selectively eliminating cytotoxic T cells," i.e., eliminating CTL preferentially, or at a higher percentage, than other types of T cells.

B) Claim 2 is vague and indefinite as it is nonsensical. Note that the claim recites the need for an action (DLI), which should follow another action, however, allogenic T cell-depleted HSC is a composition, not an action, thus, the claim is nonsensical.

C) "the HSC" in line 4 of Claim 5 has no antecedent basis in the claim.

8. Applicant is advised that due to significant differences between the disclosures of the instant application and U.S. Provisional Application No. 60/188,391, the benefit of priority of the filing date of the '391 application is denied. For example, the '391 application discloses only a method of preventing GVHD in mammals whereas the instant application recites claims drawn to the inhibiting of GVHD (Claim 1), particularly in humans (Claim 4). Additionally, the '391 application fails to disclose the separation step a) of Claim 5.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Rosenfeld et al. (1995, IDS).

Rosenfeld et al. teaches a method of inhibiting graft versus host disease (GVHD) in a human requiring donor lymphocyte infusion (DLI) comprising contacting donor lymphocytes to be infused with an aqueous solution containing a therapeutically effective amount of L-leucyl-L-leucine methyl ester (LLME) *ex vivo*, eliminating selective cytotoxic T-cells, infusing said lymphocytes into the human, and inhibiting GVHD (see Methods and Materials, page 679, column 2 - page 680, column 1). Note that the limitation of Claim 1, "a mammal in need of DLI" is met given the teaching that the patients in the reference have received total body irradiation and would therefore die absent an infusion of donor lymphocytes.

The reference clearly anticipates the claimed invention.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c)and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenfeld et al. (1995, IDS) in view of Small et al. (1999, IDS) and U.S. Patent No. 5,668,112 (1997, IDS).

Rosenfeld et al. has been discussed above. In addition to the previously described teachings, the reference also teaches that many stem cell transplantation patients suffer and die from opportunistic infections such as CMV or Aspergillus infection (see particularly Table 4). The reference also teaches that LLME treatment may cause some reduction in the number of CFU-GM (see particularly page 682, column 1, paragraph 1). The reference differs from the claimed invention in that it does not teach DLI after donor stem cell engraftment (Claim 3) nor the separation of CD34+ and CD34- cells before the LLME treatment of the CD34- cells only (Claim 5).

Small et al. teaches that the risk of opportunistic infection in stem cell transplant patients correlates with CD4 T cells in a patient, i.e., low CD4 counts increase the risk of infection (see particularly Abstract and page 474, column 1).

The '112 patent teaches that NK cells and cytotoxic T cells are primarily responsible for GVHD after DLI (see particularly column 9, lines 17-51). The reference further teaches that *ex vivo* Leu-Leu-OMe (LLME) treatment can be used to selectively kill

NK and cytotoxic T cells before DLI (see particularly column 4, lines 4-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to infuse LLME-treated donor lymphocytes into a mammal after stem cell transplantation, in view of the combined teachings of Rosenfeld et al., Small et al., and the '756 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to infuse LLME-treated donor lymphocytes into a mammal after stem cell transplantation because said mammals would be in need of the additional infusion to fight opportunistic infections, as taught by Rosenfeld et al. Given that low CD4 T cell counts increased the risk of opportunistic infection, as taught by Small et al., and increased CD8 and NK cell counts increased the risk of GVHD, as taught by the '112 patent, one of ordinary skill in the art at the time the invention was made would have been motivated to use LLME-treated donor lymphocytes because said lymphocytes would have been increased in CD4 cells, in particular, said increase would have been achieved without the additional increase in the now depleted CD8 and NK cells, and would thus, have increased the ability to ward off opportunistic infection without increasing the risk of GVHD. Claim 5 is included in the rejection because it would also have been obvious in view of the combined references to separate the cells for transplantation into CD34+ (stem cell) and CD34- (nonstem cell) fractions before LLME treatment, and treat only the CD34- fraction (the fraction comprising NK and cytotoxic T cells) while leaving the CD34+ fraction (the fraction comprising the stem cells that differentiate into CFU-GM) untreated, thus obtaining the benefits of NK and cytotoxic T cell reduction (as set forth above) without concurrent CFU-GM reduction.

14. No claim is allowed.

15. References AD and AE on the Form 1449 submitted 1/29/02 have been lined through and have not been considered because they have not been provided in their entirety. Only the first column of reference AD, and the first page of reference AE, have been provided.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the

examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
August 19, 2002